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Please provide the following:

TI Characterization of the Wistar-Kyoto rat  
bred and selected by forced swim test.

AU Will, C. C. (1); Aird, F. (1); Redei, E. (1)

SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2625.

TI Inheritance of forced swim test (FST) behaviors and hypothalamic-pituitary-adrenal (HPA) function in a F344XWKY cross.

AU Solberg, L. C. (1); Ahmadiyah, N. (1); Baum, A. E. (1);

SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2625.

TI Depressive behavior and stress ulcer in Wistar Kyoto rats.

AU Pare W P; Redei E

SO JOURNAL OF PHYSIOLOGY, PARIS, (1993) 87 (4) 229-38.

SEARCHED

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COMPLETED

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## 985.7

**ABNORMAL EMOTIONAL BEHAVIORS AND AGE-RELATED OBESITY IN 5-HT TRANSPORTER DEFICIENT MICE.** A. Holmes<sup>1</sup>, R.J. Yang<sup>1</sup>, D.L. Murphy<sup>2</sup> and J.N. Crawley<sup>1</sup>. *1. Section on Behavioral Pharmacology, NIMH, Bethesda, MD, USA. 2. Laboratory of Clinical Science, NIMH, Bethesda, MD, USA.*

The serotonin transporter (5-HTT) is a key regulator of serotonergic activity and the target of drug treatments for psychiatric disorders. 5-HTT-deficient mice have increased extracellular 5-HT and reduced 5-HT receptor number/function, but show normal health, sensory function and neurological reflexes. 5-HTT-deficient mice show increased anxiety-like behavior in 4 tests: elevated plus-maze, light/dark exploration, emergence test, and open field. Salient to an anxiety-like phenotype, mutant mice show reduced sensitivity to PTZ-induced seizure, suggesting an alteration in GABA receptor function. 5-HTT-deficient mice backcrossed onto a 129S6, but not a C57BL/6J, background show reduced depression-related immobility in the tail suspension test. Genotype differences in a second test for depression-related behavior, the forced swim test, were complicated by a neuromuscular impairment in mutant mice. Ongoing studies are testing whether 5-HTT-deficient mice are differentially sensitive to the anti-depressant effects of SSRIs. 5-HTT-deficient mice show age-related obesity. Daily food consumption was not significantly different between mutant mice and wild type littermates. Measurement of home cage activity over a 24 hour period suggests that reduced energy expenditure may lead to obesity in 5-HTT-deficient mice. To examine meal patterns in greater detail, an analysis of the microstructure of feeding behavior is being conducted. 5-HTT-deficient mice represent a model system for studying how naturally-occurring 5-HTT gene mutations and pharmacological targeting of the 5-HTT produce effects on behavior. (Supported by the NIMH Intramural Research Program).

## 985.9

**THE L1 KNOCKOUT MOUSE EXHIBITS IMPAIRED PREPULSE INHIBITION OF THE ACOUSTIC STARTLE RESPONSE.** I.K. Needham<sup>1</sup>, K.L. Miller<sup>1</sup> and P.F. Maness<sup>1</sup>. *1. Dept. of Biochemistry, University of North Carolina School of Medicine, Chapel Hill, NC, USA.*

The cell adhesion molecule L1 functions to regulate migration of neurons and growth of axons during development. L1 gene mutations are present in humans with the X-linked mental retardation syndrome termed CRASH (corpus callosal hypoplasia, retardation, adducted thumbs, spastic paraparesis, hydrocephalus). L1 knockout (KO) mice display related phenotypes. In addition, L1-KO mice display stereotypic circling behavior, a feature associated with dopaminergic dysfunction, and altered distribution of dopaminergic neurons in the mesencephalon. Prepulse inhibition (PPI) of the reflex acoustic startle response (ASR) is the reduction in ASR magnitude when the startling pulse is preceded by a weak prepulse and is an operational measure of sensorimotor gating. PPI is sensitive to dopamine manipulations: dopamine agonists induce decreased PPI. Therefore, we analyzed the ASR and PPI in L1-KO mice. L1-KO mice exhibit a decrease in both the ASR and in PPI. L1-KO (male) mice exhibited an ASR to a 50 dB stimulus that was reduced by 40% relative to littermate control male wild-type (WT) mice ( $P < 0.005$ ). When weak prepulses of 3 and 9 dB were used, the PPI of L1-KO mice was also reduced by 40% relative to WT ( $P < 0.04$ ; WT PPI = 43% at 3 dB and 40% at 9 dB). However, a stronger prepulse of 15 dB elicited PPI in L1-KO mice that was indistinguishable from WT (WT PPI = 44%). These results suggest that L1-KO mice exhibit impaired auditory sensorimotor processing as well as impairments in sensorimotor gating. It will be of interest to determine if the deficits in PPI in the L1-KO mice can be normalized with dopamine antagonists. Supported by NIH grant HD35170 and NARSAD.

## 985.8

**TORSINA IN PC12 CELLS: PRIMARY ER LOCALIZATION AND RESPONSE TO OXIDATIVE STRESS.** C. Kamm<sup>1</sup>, J. Hewett<sup>1</sup>, P.A. Ziefer<sup>1</sup>, D. Bergeron<sup>1</sup>, H. Boston<sup>1</sup>, T. Naismith<sup>2</sup>, L.J. Ozelius<sup>3</sup>, V. Ramesh<sup>1</sup>, P.J. Hanson<sup>2</sup> and X.O. Breakfield<sup>1</sup>. *1. Mol. Neurogen., Mass. Gen. Hosp., Charlestown, MA, USA. 2. Washington University, St. Louis, MO, USA. 3. Mol. Gen., Albert Einstein Coll. Med., Bronx, NY, USA.*

In-frame deletions in the carboxy terminal region of torsinA are the main cause of early-onset torsion dystonia. The TOR1A gene is expressed at high levels in dopaminergic neurons in the human brain, and preliminary studies point towards a possible role for torsinA in ER membrane trafficking. Conserved functional domains between torsinA and the AAA+ family of chaperone proteins further raise the possibility that torsinA might act as a molecular chaperone to protect cells from stress. In this study, the levels and intracellular distribution of torsinA were evaluated using a model neuronal-like cell line, rat PC12. In NGF-differentiated PC12 cells, torsinA co-localized with the luminal ER protein, protein disulfide isomerase (PDI), and the vesicular marker, synaptobrevin (VAMP), extending throughout the processes with accumulation at varicosities. Levels of torsinA did not increase in response to heat shock or various ER stress conditions. In contrast, hydrogen peroxide treatment caused a rapid upward shift in molecular weight and an apparent increase in levels of torsinA protein by western blot analysis with a marked localization in the perinuclear region by immunocytochemistry. These studies are consistent with a role for torsinA in an ER-based response to oxidative stress. Given that torsinA expression is highest in dopaminergic neurons and that dopamine itself can cause oxidative stress, wild-type torsinA may serve a protective function. Supported by NIH 28384.

## 985.10

**CHARACTERIZATION OF THE WISTAR KYOTO RAT BRED AND SELECTED BY FORCED SWIM TEST.** C.C. Will<sup>1</sup>, F. Aird<sup>1</sup> and E. Redei<sup>1</sup>. *1. Psychiatry & Behavioral Sciences, Northwestern University, Chicago, IL, USA.*

The Wistar Kyoto rat (WKY) demonstrates endogenous hormonal and behavioral abnormalities that mimic those found in symptoms presenting depressive patients. When compared to other rat strains, WKY have a prolonged circadian peak of plasma corticosterone (CORT) and elevated levels of plasma TSH and T4. WKY also exhibit decreased activity in the open field test (OFT), greater immobility in forced swim test (FST), and FST immobility is reversed by chronic antidepressant treatment. However, genetic and behavioral evidence suggest that WKY may not be truly inbred. DNA fingerprinting has shown variability both between vendors and within populations. WKY also exhibit a wider range of behavior in FST and OFT than other inbred, or even outbred rat strains. We have taken advantage of this variability of behavioral phenotype by selectively breeding WKY for 'depressive' behavior using floating and climbing behavior in the FST as a functional selector. This breeding resulted in animals that exhibit extremes of FST behavior: WKY 'most immobile' (WMI, F3 mean immobility 17±1) and WKY 'least immobile' (WLI, F4 mean immobility 8±1). Male WMI also show significantly decreased activity and a trend of decreased rearing in OFT. Sub-acute treatment with desipramine (10mg/kg) decreased FST immobility of WMI significantly more than WLI, while fluoxetine (10mg/kg) had no significant effect on either. In contrast to the behavior, there were no differences in plasma CORT or T4 levels between WMI and WLI at a time when WKY differ from other strains. These data show that WMI and WLI differ behaviorally but not hormonally, making them a very useful tool in drug discovery. Supported by NIH grant MH 60789.

## 985.11

**INHERITANCE OF FORCED SWIM TEST (FST) BEHAVIORS AND HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) FUNCTION IN A F344 X WKY CROSS.** L.C. Solberg<sup>1,2</sup>, N. Ahmadiyeh<sup>1</sup>, A.E. Baum<sup>1</sup>, M.H. Vitaterna<sup>1,3</sup>, J.S. Takahashi<sup>1,3</sup>, F.W. Turek<sup>2</sup> and E. Redei<sup>1</sup>. *1. Psychiatry & Behav. Sci., 2. Neurobiology & Physiology, 3. Howard Hughes Medical Inst., Northwestern Univ., Chicago, IL, USA.*

Wistar Kyoto (WKY) rats exhibit depressive-like behavior in the FST relative to several other rat strains, including Fischer 344 (F344) rats. In addition, WKY rats show altered HPA function consistent with a chronic stress state, larger adrenals and blunted corticosterone stress response, specifically in females. To study the genetic basis of these abnormalities in the WKY rat we mated, through reciprocal crosses, F344 and WKY rats to obtain ~120 F1 generation animals. Phenotypes, narrow sense heritability ( $h^2$ ) and mode of inheritance differed between the sexes. In the FST, immobility  $h^2 = 0.33$  in males, not heritable in females; climbing  $h^2 = 0.15$  in males and 0.34 in females. FST measures were inherited in a dominant fashion, where F1 animals exhibited behaviors similar to that of the F344 parent. For basal plasma corticosterone (CORT),  $h^2 = 0.31$  in males with a F344 dominance, with no heritability seen in females. Heritability of CORT stress response was  $h^2 = 0.18$  and 0.11, and of normalized adrenal weights was  $h^2 = 0.21$  and 0.44, in males and females, respectively, with a F344 dominance only in females. These data show that FST behaviors and HPA axis function are heritable in a gender-specific manner. No correlations were found between FST behaviors and HPA function measures, indicating that there is likely to be no genetic relationship between FST behavior and HPA activity in a WKYxF344 cross. Supported by NIH MH60789.

## 985.12

**X-LINKED INHERITANCE OF COPING STRATEGIES IN THE DEFENSIVE BURYING PARADIGM.** N. Ahmadiyeh<sup>1</sup>, L.C. Solberg<sup>1</sup>, K. Shimomura<sup>2</sup>, J.S. Takahashi<sup>2</sup> and E. Redei<sup>1</sup>. *1. Department of Psychiatry & Behavioral Sciences, Northwestern University Medical School, Chicago, IL, USA. 2. Howard Hughes Medical Institute, Department of Neurobiology and Physiology, Northwestern University, Evanston, IL, USA.*

Differences in coping strategies elicit simultaneous changes in physiological variables with bearing on chronic disease, and extreme coping styles can influence susceptibility to psychiatric disorders. Human studies suggest that at least some aspects of coping behaviors are under genetic control, but animal studies of the transmission of coping behaviors hold more molecular genetic potential and have as yet been unattempted. The defensive burying (DB) test, although originally developed as a test of anxiety, can accurately measure differences in coping strategies by assaying an animal's behavioral response to an immediate threat with ethological validity. Using offspring derived from reciprocal crosses of two inbred rat strains (Wistar Kyoto and Fischer 344) differing on DB behaviors, we show that coping styles are inherited in an X-linked fashion, with heritability estimates of 0.29 - 0.41 for different DB behaviors. We find that first generation (F1) males but not females show maternally-derived coping styles, and second generation (F2) females but not males show significant differences in coping styles depending on strain of grandmother, strongly suggestive of X-linkage for this trait. Quantitative trait loci analysis will be useful in identifying genetic loci responsible for different DB behaviors as well as in confirming X-linkage. Supported by NIH MH60789.